REMARKS

Claims 24 and 27 have been canceled without prejudice. Claims 14, 16, 17, 22, 23, 25, 26, 28 - 38 have been amended. Claims 39 – 44 have been added. Claims 14, 16, 17, 22, 23, 25, 26, 28 - 44 are now pending. Support for each pending claim is listed in Table I.

Priority

This application was filed under 35 U.S.C. § 371 of PCT/US03/37963 (filed on November 26, 2003), which claims priority as a continuation-in-part of co-pending U.S. Patent Application No. 10/306,614 ("'614 application") filed on November 26, 2002. The disclosure of the '614 application is incorporated by reference in the present application.

The Examiner states that "claims 14, 16, 17 and 22-38 do not obtain the benefit of the earlier filed '614 application [and that] [t]he effective filing date for the instant claims 14, 16, 17 and 22-38 is 11/26/2003." Office Action, pg 4.

In order to be entitled to an earlier priority date, each claim limitation must be expressly, implicitly or inherently supported in the originally filed disclosure. (Guidelines for Examination of Patent Applications Under 35 U.S.C. §112, ¶ 1, "Written Description" Requirement, 60 Fed. Reg. 1099, 1106-7 (Jan. 5, 2001); M.P.E.P. § 2163.)

Applicants respectfully submit that, as shown in Table I, support for claims 14, 16, 17, 22, 23, 26, 28, 29 and 31 - 38 can be found in the specification of the '614 application and that the priority date for these claims is November 26, 2002, the filing date of the '614 application.

Table I: Support for Pending Claims

Claim No.	Support in U.S. Application No. 10/306,614 (Paragraph No.)	Support in U.S. Application No. 10/536,569 (Paragraph No.)
14	0147 (see also Table I)	
16	0037, 0161 (see also Table I)	
17	0012	
22	0042	
23	0044, 0045	
25		0033, 0045
26	0147 (see also Table I)	
28	0037, 0161 (see also Table I)	
29	0045	
30		0033, 0045
31	0017, 0044, 0133-0135	
32	0012	
33	0145	
34	0045	
35	0045	
36	0017, 0044, 0133-0135	
37	0012	
38	0042	
39	0149	
40	0149	
41	0149	0044[1]
42		0044
43		0044
44		0044

[1] Single particle size was measured by fluorescence correlation spectroscopy (paragraph 0042 of the present application). Within the bounds of the level of precision of fluorescence correlation spectroscopy, the lower end of 1.6 nm is the mean radius of the core of the compact core/shell particle, minus two standard deviations (0.3 nm SD). The upper end of 3.5 nm is the mean radius of the core of the expanded core/shell particle, plus two standard deviations (0.3 nm SD).

35 U.S.C. § 112 New Matter Rejections

Claims 14, 16, 17 and 22-38 stand rejected under 35 U.S.C. § 112, first paragraph, as not complying with the written description requirement (Office Action, pg. 6).

Table I shows where support for each pending claim can be found in the '614 application or in the present application. No new matter has been added and Applicants request that the rejection of the pending claims under 35 U.S.C. § 112, first paragraph, be withdrawn.

Information Disclosure Statement

The Examiner states that, in the Supplemental Information Disclosure Statement filed on June 20, 2006, the first reference by Ow (hereinafter "Ow") listed on page 2 "does not appear to be listed in the IDS form, and it is also not clear if a copy of the said reference was provided" (Office Action, pg. 4).

Applicants respectfully submit that Ow was listed in the Information Disclosure Statement ("IDS") filed on February 28, 2006 as item G under Non-patent Literature Documents, which the Examiner has already considered. However, for the Examiner's convenience, Applicants hereby re-submit a copy of Ow.

The Examiner has also required the date information for "Srivastava, Mamta et al" (item H in the IDS filed on February 28, 2006). Applicants hereby submit a new IDS listing this reference with the correct date information.

Oath/Declaration

The Examiner considers the oath or declaration to be defective (Office Action, pg. 5). Applicants submit herewith a new Declaration in compliance with 37 CFR 1.67(a).

35 U.S.C. § 102(b) Rejection

Claims 14, 16, 17, 22-28 and 30-32 stand rejected under 35 U.S.C. §102(b) as being anticipated by Graf et al. *Langmuir*, 1999, Vo1.15, pages 6170-6180 (hereinafter, "Graf").

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicants respectfully submit that Graf fails to teach or suggest every limitation of the claims.

The Examiner states that Graf "teaches silica nanoparticles ... with silica core and silica shell and functional groups for attaching various organic fluorescent dyes to the silica core or within the silica core" (Office Action, pg. 7). Applicants respectfully submit that, to the contrary, Graf does not teach the use of a fluorescent silica-based nanoparticle comprising a fluorescent organic dye covalently conjugated to either a silica-based nanoparticle or a silica-based core as set forth in all the pending claims. Rather, Graf discloses poly(organosiloxane) microgels with core-shell architecture (see, for example, article title, abstract and Figure 1). Silica, also referred to as silicon dioxide, has the chemical formula SiO_2[2], while polysiloxanes have an -Si-O-Si-O- backbone, rather than SiO_2.[3] Applicants therefore assert that Graf fails to teach a silica-based nanoparticle or a silica based core.

Accordingly, Graf does not disclose all of the elements of the pending claims. Thus, the pending claims are not anticipated by Graf. Applicants respectfully request that the rejection of the pending claims under 35 U.S.C. § 102(b) be withdrawn.

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[2] "Silica." Webster's Third New International Dictionary, Unabridged. Merriam-Webster, 2002 ("[T]he chemically resistant dioxide SiO_2 of silicon..."). [Attachment A]

[3] "Siloxane." Webster's Third New International Dictionary, Unabridged. Merriam-Webster, 2002 ("[A]ny of a class of compounds that contain alternate silicon and oxygen atoms in either a linear structure [as $H_3Si(OSiH_2)_nOSiH_3$] or a cyclic structure [as $(H_2SiO)_n$]....) [Attachment B]

35 U.S.C. § 103(a) Rejections

Claims 14, 16, 17, 22-32 and 34-38 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Graf in view of U.S. Patent No. 6,132,773 to Amiche (hereinafter "Amiche"), and if necessary in view of van Blaaderen et al. *Langmuir*, 1992, Vol.8, pages 2921-2931 (hereinafter "van Blaaderen").

Claims 14, 16, 17 and 22-38 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Graf, Amiche and van Blaaderen, and further in view of U.S. Patent Publication No. 2002/0048800 by Gu (hereinafter "Gu").

Claims 14, 16, 17 and 22-38 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Graf, Amiche, van Blaaderen and Gu, and, if necessary, in view of U.S. Patent No. 6,207,392 to Weiss et al. (hereinafter "Weiss").

For the reasons discussed below, the Applicants assert that the rejected claims are not obvious over the cited combinations of art and respectfully request withdrawal of such rejections.

I. Graf and Amiche

With respect to claims 14, 16, 17, 22-32 and 34-38, the Examiner states that Graf does not teach the thickness of the silica shell as recited in claims 29, 34 and 35, however, van Blaaderen et al teach "a layer of any desired thickness of silica...", and therefore, "it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use silica based "core-shell" structured nanoparticles with various silica shell thickness such as 25 nm to 100 nm" (Office Action, pg. 10).

Applicants respectfully submit that Graf does not teach the use of a fluorescent silica-based nanoparticle comprising a fluorescent organic dye covalently conjugated to either a silica-based nanoparticle or a silica-based core. As pointed-out above, Graf discloses poly(organosiloxane) microgels with core-shell architecture. The combination of Graf, Amiche and van Blaaderen does not change the fact that the nanoparticles of Graf are not silica-based nanoparticles.

Furthermore, Amiche teaches particles with a silica shell and a core comprising material other than silica (see, for example, Abstract and Col. 1, ll. 8 - 12), while the nanoparticles claimed in the present invention comprise silica-based core.

The Examiner goes on to state that "because both van Blaaderen and the Amiche reference teach methods of using various nanoparticles with various shell thickness, it would have been obvious to one skilled in the art to substitute one type of silica shell thickness for the other to achieve the predictable result of detecting analytes in samples based on fluorescence silica nanoparticles." (Office Action, pg. 10). In addition, the Examiner states that "all of the techniques for generating the silica based nanoparticles with various functional groups … are known and routine" and that therefore, a person of ordinary skill in the art would have a reasonable chance of success. Id. at 11. As discussed further below, Graf cannot be modified to produce the ligated shells of the present claims. Therefore, there would not have been any reasonable expectation of success if the references were modified in order to achieve the desired fluorescent silica-based nanoparticles.

II. Graf, Amiche and van Blaaderen in view of Gu

With respect to claims 14, 16, 17 and 22-38, the Examiner states that, "[a] person of ordinary skill in the art would have been motivated at the time of the invention to use a maleimide functional containing dye to label nanoparticles, because Gu et al teach the convenience of using commercially available fluorescent dyes." Office Action, pg 12. As discussed previously, Graf does not teach the use of a fluorescent silica-based nanoparticle comprising a fluorescent organic dye covalently conjugated to either a silica-based nanoparticle or a silica-based core. The combination of Graf, Amiche and van Blaaderen does not change the fact that the nanoparticles of Graf are not silica-based nanoparticles. Moreover, as discussed further below, the nanoparticles of Graf are inert and therefore, cannot be modified. Therefore, there would not have been any reasonable expectation of success if the references were modified in order to achieve the desired fluorescent silica-based nanoparticles.

III. Graf, Amiche, van Blaaderen and Gu in view of Weiss

With respect to claims 14, 16, 17 and 22-38, the Examiner states that although the combination of Graf, Amiche, van Blaaderen and Gu does not teach the ligand is a biological molecule, Weiss teaches "conjugating affinity molecules (read on ligands onto nanocrystals (or nanoparticles)" (Office Action, pg. 13). The Examiner goes on to state that "it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to generate silica based "core-shell" structured nanoparticles with attached biological molecules as ligands" (Id. at 14).

As discussed above Graf does not teach the use of a fluorescent silca-based nanoparticles comprising a fluorescent organic dye covalently conjugated to either a silica-based nanoparticle or a silica-based core. The combination of the various references here does not change this structural fact.

The Examiner states that when combining Graf, Amiche, van Blaaderen and Gu with Weiss, "[a] person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications" (Office Action, pg. 14).

To the contrary, the Applicants submit that Graf cannot be modified to produce the ligated shells of the present claims. The Graf core-shell particles are synthesized in a multi-step reaction (see, for example, Figure 1 and Experimental Section). The first step is the synthesis of the functional core. "In the second step, a nonfunctional shell is formed by addition of a variable amount of M1(nonfunctionalized monomer)" (pg 6171, last paragraph of the left column). Then the preformed core-shell particles are coated in an "endcapping reaction" with a hydrophobic surface. Graf teaches that "[d]uring the endcapping step, all reactive Si-OH moieties should be converted into inert Si-O-$Si(CH_3)_3$ groups by reaction with M3 (first step) or HMN (second step). If this conversion is not complete, partial interparticle aggregation may occur" (pg. 6174). Thus, to obtain stable particles only functionalized with dye in the core, the outer shell of the Graf particles is inert, as disclosed in Graf as "an unfunctionalized protective shell" (pg. 6179, first paragraph under Conclusion). If the particle surface is inert, however, standard reaction schemes as disclosed by Weiss to attach a ligand to the particle surface

cannot be applied. Therefore, there would not have been any reasonable expectation of success when the references were modified.

Furthermore, the fluorescence of Weiss is dictated by the physical properties of the nanocrystals of the core itself, rather than an organic compound linked to the core. A silica-based core, in particular, is contrary to the nanocrystal core of Weiss as one of ordinary skill in the art understands that silica is fundamentally and inherently amorphous rather than crystalline. For example, an amorphous silica-based core is incompatible with the quantum-confined, crystal-based emission characteristics that characterize the specific, selectable emission spectra of Weiss: "the frequency or wavelength of the narrow wavelength band of light emitted from the semiconductor nanocrystal may be further selected according to the physical properties, such as size, of the semiconductor nanocrystal." Weiss at column 8, lines 34-38. Accordingly, Graf cannot be modified in view of Amiche, van Blaaderen since the principle of operation of Graf is incompatible with the silica-based nanoparticle or silica-based core composed of an organic fluorescent compound.

Nonstatutory Obviousness Type Double Patenting Rejection

Claims 14, 16, 22-24, 26, 28 and 31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 48, 60, 62, 64 and 66 of the '614 application. Office Action, pg. 15.

In order to expedite the prosecution, but not wishing to agree on the substantive basis of the Examiner's rejection, the Applicant will consider submitting the requested terminal disclaimer in compliance with 37 CFR § 1.321(b) upon recognition of allowance of the pending claims. The Applicant respectfully point out that the present application and the '614 application are commonly owned.

CONCLUSION

Given the foregoing, Applicants respectfully submit that all pending claims are in condition for allowance. Favorable action is earnestly solicited.

Applicants believe no additional fees are due. However, the Commissioner is hereby authorized to deduct any fees due from Deposit Account No. 01-3050 if there is a deficiency.

Respectfully submitted,
Axinn Veltrop & Harkrider LLP

By:___/Michael A. Davitz/_____

June 19, 2009

Michael A. Davitz M.D. J.D.
Reg. No. 47,519
Customer No. 67272
114 West 47th Street
New York, NY 10036
Tel.: (212) 728-2236

Attachment A

9 entries found.

silica
fused quartz
silica aerogel
silica brick
silica cement
silica gel
silica glass
silica ware
vitreous silica

To select an entry, click on it. Click 'Go' if one entry is listed.

Go

Double-click any word in the entry to see its definition.

Main Entry: **sil·i·ca** Pronunciation Guide
Pronunciation: ˈsilə̇kə, -ˌlēkə
Function: *noun*
Inflected Form(s): **-s**
Etymology: New Latin, from Latin *silic-*, *silex* hard stone, flint, quartz -- more at SHELL
: the chemically resistant dioxide SiO_2 of silicon that occurs naturally in the three crystalline modifications of quartz, tridymite, and cristobalite, in amorphous and hydrated forms (as opal), and in less pure forms (as sand, diatomite, tripoli) and combined in silicates , that can be prepared artificially as a fine white powder from water glass or other soluble silicates and also in colloidal form, and that is used chiefly in making glass, ceramic products, and refractories, in producing elemental silicon , its alloys, and compounds, and as an abrasive, adsorbent, and filler

Citation format for this entry:
"silica." *Webster's Third New International Dictionary, Unabridged.* Merriam-Webster, 2002. http://unabridged.merriam-webster.com (21 Jan. 2009).

Attachment B

One entry found.

siloxane

Click Here to view Previous Lists

Double-click any word in the entry to see its definition.

Main Entry: **si·lox·ane** Pronunciation Guide
Pronunciation: sə'läk,sān
Function: *noun*
Inflected Form(s): **-s**
Etymology: blend of *silane* and *oxygen*
: any of a class of compounds that contain alternate silicon and oxygen atoms in either a linear structure [as $H_3Si(OSiH_2)_nOSiH_3$] or a cyclic structure [as $(H_2SiO)_n$] and that in many cases contain methyl, phenyl, or other organic radicals in place of some or all of the hydrogen atoms and are made by hydrolysis of chlorosilanes or alkoxy-silanes -- see SILICONE

Citation format for this entry:
"siloxane." *Webster's Third New International Dictionary, Unabridged.* Merriam-Webster, 2002. http://unabridged.merriam-webster.com (21 Jan. 2009).